REMARKS

I. Status Summary

Claims 1-23 were filed in the subject application. Claims 18, 19, 22, and 23 have been withdrawn pursuant to the September 28, 2006 Response to the August 28, 2006 Restriction Requirement issued by the U.S. Patent and Trademark Office (hereinafter "the Patent Office"). Accordingly, claims 1-17, 20, and 21 have currently been examined and are pending in the Patent Office.

The Patent Office has acknowledged applicants' claim for foreign priority, based on Australian Patent Application No. 2003/901425. However, the Patent Office asserts that a certified copy of the priority application has not been filed with the Patent Office, as required by 35 U.S.C. §119(b).

The Patent Office asserts that the references cited in the specification of the subject application do not constitute a proper Information Disclosure Statement.

Table 1 of the specification has been objected to by the Patent Office as allegedly lacking SEQ ID NO identifiers.

The Patent Office further asserts that the subject application contains sequences that are not identified by SEQ ID NOs and are not contained in the sequence listing of the application.

The Patent Office has objected to claims 1-17 and 20 in view of several asserted claim informalities. Particularly, the Patent Office asserts that claim 1 lacks a step (c), the term "or" can be removed from step (d) of claim 3, claims 4 and 21 recite non-elected subject matter, the term "an" can be removed from claim 21, and claim 6 is of improper dependent form for failing to further limit the subject matter of a previous claim.

Claims 1-17, 20, and 21 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

The Patent Office has rejected claims 1-17, 20, and 21 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 1-17, 20, and 21 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Patent Office has rejected claims 1-3, 5-10, 12, 16, and 20 under 35 U.S.C. §102(b) as allegedly being anticipated by Claes *et al.* (2001) *Am J of Human Genet* **68**:1327-1332 (hereinafter referred to as "Claes *et al.*").

The Patent Office has rejected claims 11, 13-15, and 17 under 35 U.S.C. §103(a) as allegedly being unpatentable over Claes *et al.* in view of U.S. Patent No. 6,331,614 to Wong *et al.* (hereinafter referred to as "Wong *et al.*").

Claims 1, 2, 6, 11, and 21 have been amended herein. Support for the amended claims can be found throughout the specification as filed, including particularly at page 4, lines 28-33; page 5, lines 2-25; page 37, line 29, through page 38, line 5; and in Figure 1. No new matter has been added.

New claims 24 and 25 have been added herein. Support for new claims 24 and 25 can be found throughout the specification as filed, including particularly at page 5, lines 13-21; page 42 lines 3-9; and in independent claim 1 as originally filed. No new matter has been added.

Reconsideration of the application based on the arguments set forth herein is respectfully requested.

An Information Disclosure Statement is being filed concurrently herewith. It is requested that the reconsideration of this application include consideration of the documents cited in that statement.

II. Response to the Objection to the Priority Claim

The Patent Office has acknowledged applicants' claim for foreign priority, based on Australian Patent Application No. 2003/901425. However, the Patent Office has asserted that a certified copy of the priority application has not been filed with the Patent Office, as required by 35 U.S.C. §119(b).

In response, applicants submit herewith a certified copy of the priority application, Australian Patent Application No. 2003/901425. Accordingly, applicants respectfully request that the instant objection to the priority claim be withdrawn at this time.

III. Response to the Information Disclosure Statement Objection

The Patent Office has asserted that the references cited in the specification of the subject patent application do not constitute a proper Information Disclosure Statement. Particularly, the Patent Office asserts that 37 C.F.R. §1.98(b) states that the list of all patents, publications, and other information to be considered by the Patent Office cannot be incorporated into the specification of the patent application, but must be submitted in a separate paper. Accordingly, the Patent Office asserts that unless the references were cited by the Examiner, they have not been considered.

In response, applicants respectfully submit that the references considered most pertinent have been disclosed to the Patent Office by way of three Information Disclosure Statements submitted on April 22, 2004; June 25, 2004; and September 6, 2006, and thus have been considered by the Patent Office. However, in the spirit of cooperation, applicants submit herewith an Information Disclosure Statement disclosing the references on pages 47-49 of the subject specification that have previously not been disclosed to the Patent Office. Accordingly, applicants respectfully request that the instant objection to the Information Disclosure Statement be withdrawn at this time.

IV. Response to the Objections to the Specification

The Patent Office has objected to Table 1 of the subject specification as allegedly lacking sequence identifiers as required by 37 C.F.R. §1.821(d).

In response, Applicants submit herewith an amended Table 1 which includes the required SEQ ID NOs, as set forth hereinabove. Applicants further submit that a Sequence Listing Statement has been included herewith verifying that the Sequence

Listing information recorded in computer readable form is identical to the written Sequence Listing (on paper). No new matter has been added. Accordingly, applicants respectfully request that the instant objection to the specification be withdrawn at this time.

V. Response to the Objection to the Sequence Listing Statement

The Patent Office asserts that Table 1 of the subject application contains sequences that are not identified by SEQ ID NOs and are not contained in the sequence listing of the application. Thus, the Patent Office asserts that a new Sequence Listing must be provided.

In response, applicants respectfully submit that a new Table 1 has been provided herewith that incorporates the appropriate SEQ ID NOs, as indicated hereinabove. Applicants submit that a CRF copy and a paper copy of the amended sequence listing is also provided herewith. Applicants further submit that the previous sequence listing and Table 1 have been deleted from the specification and an amended sequence listing and amended Table 1 inserted in place thereof, respectively, as indicated hereinabove. No new matter has been added. Accordingly, applicants respectfully request that the instant objection to the Sequence Listing Statement be withdrawn at this time.

VI. Response to the Objection of Claims 1-17 and 20

VI.A. Response to the Objection of Claim 1

The Patent Office has objected to claim 1 under the assertion that steps (a), (b) and (d) are listed without a corresponding step (c) in claim 1. In addition, the Patent Office asserts that the term "or" should be deleted from the phrase "or, if not known to be either" in step 3(d).

In response, applicants respectfully submit that the numbering of step (d) has been amended to step (c). In addition, the phrase "or, if not known to be either" in step 3(d) has been omitted. Accordingly, applicants respectfully request that the Patent Office objection to claim 1 be withdrawn at this time.

VI.B. Response to the Objection of Claim 4

The Patent Office has objected to claim 4 as allegedly reciting non-elected subject matter. Particularly, the Patent Office asserts that in view of the restriction requirement election of the c251A→G nucleotide change, claim 4 should be narrowed.

In response, applicants submit that the Patent Office contention that claim 4 allegedly contains non-elected subject matter is premature, as the non-elected subject matter relates to non-elected species, and as such the non-elected subject matter is rejoinable if and when a generic claim is deemed allowable. Accordingly, applicants respectfully request that the Patent Office objection of claim 4 be withdrawn at this time.

VI.C. Response to the Objection of Claim 21

The Patent Office has objected to claim 21 as allegedly reciting non-elected subject matter. Particularly, the Patent Office asserts that in view of the restriction requirement election of the c251A→G nucleotide change, claim 21 should be narrowed. In addition, the Patent Office asserts that claim 21 should be amended to delete the term "an" from the phrase "establishing an a diagnosis of".

In response, applicants submit that the Patent Office contention that claim 21 allegedly contains non-elected subject matter is premature, as the non-elected subject matter relates to non-elected species. Applicants further submit that the non-elected subject matter is rejoinable if and when a generic claim is deemed allowable.

Applicants further submit that the phrase "establishing an a diagnosis of" in claim 21 has been amended to recite "a diagnosis". Accordingly, applicants respectfully request that the objection to claim 21 be withdrawn at this time.

VI.D. Response to the Objection of Claim 6

The Patent Office has objected to claim 6 as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim.

Particularly, the Patent Office asserts that claim 6 does not offer any further limitation to the subject matter of claim 5.

Applicants respectfully disagree. However, in an effort to facilitate prosecution, claim 6 has been amended herein to recite, *inter alia*, "[a] method as claimed in claim 5 wherein the performing one or more assays comprises: (1) performing one or more assays to test for the existence of an alteration in the SCN1A gene of the patient; and if the results indicate the existence of an alteration in the SCN1A gene; (2) performing one or more assays to identify the nature of the SCN1A alteration." Support for the amendment to claim 6 can be found throughout the specification as filed, including particularly at page 6, line 34, through page 7, line 11. No new matter has been added. Applicants respectfully submit that the instant amendment to claim 6 addresses the allegedly improper form of claim 6. Accordingly, applicants respectfully request that the instant objection to claim 6 be withdrawn at this time.

VII. Response to the 35 U.S.C. §112, Second Paragraph, Rejection of Claims 1-17, 20, and 21

Claims 1-17, 20, and 21 have been rejected under 35 U.S.C. §112, second paragraph, on several bases as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Initially, the Patent Office asserts that claims 1, 3, 5-17, and 20 are unclear as improperly reciting the phrase "detecting an alteration in the SCN1A gene" in claim 1. Particularly, the Patent Office asserts that the metes and bounds of the claimed subject matter are not clearly defined.

In response, applicants respectfully submit that independent claim 1 has been amended herein to recite a method for determining the likelihood that a patient suspected of SMEI does or does not have SMEI, comprising, *inter alia*, testing a patient sample for the existence of an alteration in the SCN1A gene of a patient. Support for the amendment to claim 1 can be found throughout the specification as

filed, including particularly at page 4, lines 28-33; page 5, lines 2-25; page 37, line 29, through page 38, line 5; and in Figure 1. No new matter has been added.

After a review of the subject patent application, one of ordinary skill in the art at the time the application was filed would be able to ascertain the metes and bounds of the subject matter of "testing a patient sample for the existence of an alteration in the SCN1A gene." Particularly, applicants point to page 6, lines 9 through 16 of the subject specification, which recites:

> The nature of the alterations in the SCN1A gene may encompass all forms of gene mutations including deletions, insertions, rearrangements and point mutations in the coding and non-coding regions such as the promoter, introns or untranslated regions. Deletions may be of the entire gene or only a portion of the gene whereas point mutations may result in stop codons, frameshifts or amino acid substitutions.

Accordingly, applicants respectfully submit that the metes and bounds of the phrase "testing a patient sample for the existence of an alteration in the SCN1A gene" has been sufficiently defined in the instant specification, such as to encompass all forms of gene mutations, including deletions, insertions, rearrangements and point mutations compared to the normal SCN1A gene expression. Thus, applicants respectfully submit that the instant rejection of claim 1 has been addressed. Applicants further submit that claims 3, 5-17, and 20 depend from claim 1. Accordingly, the rejection of claims 3, 5-17, and 20 is also believed to have been addressed.

In response to the Patent Office's assertions that it is unclear to what the alteration is being compared, applicants particularly point to page 7, line 11, through page 8, line 17, which recites (emphasis added):

> ...an assay system employed may be the analysis of SCN1A DNA from a patient sample <u>in comparison to wild-type</u> SCN1A DNA...One such assay may look at a series of Southern blots of DNA that has been digested with one or more restriction enzymes. Each blot may contain <u>a series of normal individuals and a series of patient samples</u>. Samples displaying hybridisation fragments that differ in

> length from normal DNA when probed with sequences near or including the SCN1A gene (SCN1A gene probe) indicate a possible SCN1A alteration...SCN1A exon specific hybridisation assays may also be employed. This type of probe-based assay will utilize at least one probe which specifically and selectively hybridises to an exon of the SCN1A gene in its wild-type form. Thus, the lack of formation of a duplex nucleic acid hybrid containing the nucleic acid probe is indicative of the presence of an alteration in the SCN1A gene. Because of the high specificity of probe-based tests, any negative result is highly indicative of the presence of an SCN1A alteration however further investigational assays should be employed to identify the nature of the alteration to determine the likelihood it is an SMEI-associated alteration.

Accordingly, applicants respectfully submit that upon review of the present disclosure, one of ordinary skill in the art would understand that the alteration in the SCN1A gene is being compared to that found in normal individuals. Thus, the instant objection of claims 1, 3, 5-17, and 20 as allegedly being unclear is believed to have been addressed.

Next, the Patent Office asserts that the preamble of claims 1 and 21 indicates a method for the diagnosis of SMEI in a patient, but that there is no final step in which SMEI is actually diagnosed in the patient.

In response, applicants respectfully submit that without acquiescing the assertions of the Patent Office, independent claim 1 and claim 21 have been amended herein to recite a method for determining the likelihood that a patient suspected of SMEI does or does not have SMEI comprising, *inter alia*, establishing a likelihood of high or low probability of SMEI where an alteration in the SCN1A gene is known to be SMEI associated or non-SMEI associated, respectively. Support for the amendment to claims 1 and 21 can be found throughout the specification as filed, including particularly at page 6, lines 22-26; page 8, lines 5-17; page 14, lines 3-16; and in Figure 1. No new matter has been added. Accordingly, applicants respectfully submit that the instant rejection of independent claim 1 is believed to have been addressed. Applicants further submit that claims 2-17 and 20 depend

from independent claim 1, and as such, the instant rejection of these claims is also believed to have been addressed.

Continuing, the Patent Office asserts that the phrases "high probability" and "low probability" as recited in claims 1 and 21 indicate relative probabilities, and that it is unclear to what the probabilities are being compared.

In response, applicants respectfully submit that claims 1 and 21 have been amended herein to recite, *inter alia*, ascertaining whether the alteration, when one is detected, is known to be SMEI associated or non-SMEI associated or is not known to be either; wherein a diagnosis which will indicate a high probability of SMEI is made where the alteration is known to be SMEI associated or a diagnosis which will indicate a low probability of SMEI is made where the alteration is non-SMEI associated. Support for the amendment to claims 1 and 21 can be found throughout the specification as filed, including particularly at page 6, lines 22-26; page 8, lines 5-17; page 14, lines 3-16; and in Figure 1.

Applicants submit that after a review if the disclosure of the subject application, one of ordinary skill in the art would understand the phrase "diagnosis of a high probability of SMEI" and "establishing a likelihood of low probability of SMEI" to reference a normal population. To elaborate, a diagnosis of high probability of SMEI can be made if a patient has an alteration known to be SMEI associated. In such instances, one of ordinary skill in the art after a review of the present disclosure would understand that the patient would be more likely than a member of the normal population to have SMEI. Similarly, a diagnosis of low probability of SMEI can be made if a patient has a non-SMEI associated alteration. In such instances, one of ordinary skill in the art after a review of the present disclosure would understand that the subject would be less likely than a member of the normal population to have SMEI. Accordingly, applicants respectfully submit that the instant rejection of claims 1 and 21 has been addressed.

Additionally, the Patent Office asserts that claims 1 and 21 are unclear in view of the recitation of the phrase "known to be". Particularly, the Patent Office asserts

that it is unclear what entitles a particular mutation to be "known to be SMEI associated."

In response, applicants respectfully submit that after reviewing the specification, one of ordinary skill in the art at the time the application was filed would understand that when a particular mutation is "known to be SMEI associated", the mutation has been previously determined to be associated with SMEI. Specifically, applicants point to page 6, lines 22-33 of the subject specification, which recites:

> The identification of SCN1A alterations in a patient that lead to more severe changes to the SCN1A protein (such as frameshift mutations and nonsense mutations leading to a truncated protein) increases the likelihood that the patient has SMEI. This likelihood is increased even further if it can be shown that the alteration is a *de novo* change rather than one that is inherited from the patients parents or relatives, or that the alteration in the SCN1A gene is one that has previously been associated with SMEI. The flow chart in Figure 1 illustrates one aspect of the present invention.

Applicants further point to page 41, lines 23-33 of the specification, which recites:

> The results of the screening of 26 of the 33 amplicons of the SCN1A gene are shown in Table 3. A total of 96 patients were analysed with their clinical epilepsy phenotype being hidden during the analysis. A total of 34 samples were shown to have an alteration in the SCN1A gene and of these, 28 samples had a clear SMEI phenotype based on a clinical analysis. Four of the SCN1A alterations (M1780T, R222X, R1407X, R1892X) that were identified are not shown in Table 3 as they had previously been associated with SMEI (Nabbout et al., 2003; Claes et al., 2001; Sugawara et al., 2002).

Accordingly, applicants respectfully submit that upon review of the present disclosure, one of ordinary skill in the art would readily be able to ascertain that when a particular mutation is said to be "known to be SMEI associated", the particular mutation has been previously associated with SMEI in the art.

The Patent Office further asserts that claim 2 is unclear in view of the recitation of the phrase "a major disruption to the protein." Specifically, the Patent Office asserts that it is unclear what is included within "a major disruption".

In response, applicants respectfully submit that after reviewing the specification, one of ordinary skill in the art at the time the application was filed would understand what is intended by the phrase "a major disruption of the protein". Particularly, applicants respectfully submit that one of ordinary skill in the art would understand that a major disruption in a protein could include any alteration in the SCN1A gene that can cause a change in the protein conformation and/or function. For example, a major disruption in a protein can include truncating alterations, missense mutation, and so forth.

Further, applicants particularly point to page 42, lines 2-8 of the subject specification, which recites (emphasis added):

> In addition, based on current opinion (Mulley et al., 2003) the likelihood would further increase if the alteration is not seen in the parents or relatives of the affected individual (i.e. is a *de novo* alteration) and is still further increased if the alteration is found to result in <u>a major disruption to the protein (such as a truncating alteration).</u>

Accordingly, applicants respectfully submit that upon review of the present disclosure, one of ordinary skill in the art would readily be able to ascertain what constitutes "a major disruption to the protein", as currently recited in claim 2. Thus, applicants respectfully request that the instant rejection of claim 2 has been addressed.

Claims 2 and 3 have been rejected by the Patent Office in view of the assertion that the phrase "the protein" allegedly lacks antecedent basis.

In response, applicants submit that without acquiescing to the assertions of the Patent Office, claim 2 has been amended herein to recite, *inter alia*, "establishing whether the alteration would result in a major disruption to <u>a</u> protein." No new matter has been added. Accordingly, the instant rejection of claim 2 is believed to have

been addressed. Applicants further submit that claim 3 depends from claim 2, and as such, the instant rejection of claim 3 is also believed to have been addressed.

Further, the Patent Office asserts that claims 2 and 3 are unclear in view of the recitation of the phrase "very high probability". Particularly, the Patent Office asserts that it is unclear if "a very high probability" is meant to refer to some specific probability, or to a probability that is some particular amount higher than some other specific probability.

In response to the Patent Office's assertions, applicants respectfully submit that upon review of the disclosure of the subject specification, one of ordinary skill in the art at the time the application was filed would be able to ascertain the meaning of "a very high probability" as used in claims 2 and 3. Particularly, one of ordinary skill in the art would be able to determine that establishing a likelihood of a very high probability of SMEI refers to a notably greater than average probability of SMEI as compared to a normal population. Stated another way, a very high probability of SMEI would be understood to mean that there is a significant chance that a patient will or has developed SMEI. Accordingly, applicants respectfully submit that the instant rejection of claims 2 and 3 has been addressed.

The Patent Office asserts that claim 4 is unclear over the recitation of the phrase "wherein the alteration is one identified in Table 3" in view of the species election of the c251A→G nucleotide change.

In response, applicants respectfully submit that the Patent Office appears to be requiring applicants to limit the subject matter of claim 4 to the c251A→G nucleotide change. Applicants submit that the Patent Office contention that claim 4 should be limited as such is premature, as the subject matter relates to non-elected species, and as such the non-elected subject matter is rejoinable if and when a generic claim is deemed allowable. Accordingly, applicants respectfully submit that the instant rejection of claim 4 has been addressed.

Continuing, the Patent Office asserts that claim 11 is unclear in view of the recitation of the phrase "the sample DNA", as lacking antecedent basis.

In response, applicants respectfully submit that without acquiescing to the assertions of the Patent Office, claim 11 has been amended herein to recite "a sample DNA to be tested". No new matter has been added. Accordingly, applicants respectfully submit that the instant rejection of claim 11 has been addressed.

The Patent Office asserts that claim 21 is unclear because the preamble of claim 21 indicates a method for the diagnosis of SMEI in a patient, but that there is no final step in which SMEI is actually diagnosed in the patient.

In response, applicants respectfully submit that without acquiescing to the assertions of the Patent Office, the preamble of claim 21 has been amended herein to recite a method for determining the likelihood that a patient suspected of SMEI does or does not have SMEI, comprising, the steps for determining the likelihood that a patient does or does not have SMEI. Support for the amendment to claim 21 can be found throughout the specification as filed, including particularly at page 6, lines 22-26; page 8, lines 5-17; and page 14, lines 3-16. No new matter has been added. Accordingly, applicants respectfully submit that the instant rejection of claim 21 has been addressed.

The Patent Office asserts that claim 21 is unclear over the recitation of the phrase "alteration as laid out in Table 3" in view of the species election of the c251A→G nucleotide change.

In response, applicants respectfully submit that the Patent Office appears to be requiring applicants to limit the subject matter of claim 21 to the c251A→G nucleotide change. Applicants submit that the Patent Office contention that claim 21 should be limited as such is premature, as the subject matter relates to non-elected species. Applicants further submit that the non-elected subject matter is rejoinable if and when a generic claim is deemed allowable. Accordingly, applicants respectfully submit that the instant rejection of claim 21 has been addressed.

In summary, applicants respectfully submit that each rejection of claims 1-17, 20, and 21 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite has been addressed. Accordingly, applicants respectfully request that the instant

rejection of claims 1-17, 20, and 21 be withdrawn at this time. Allowance is also respectfully requested.

VIII. Response to the 35 U.S.C. §112, First Paragraph, Written Description Rejection of Claims 1-17, 20, and 21

The Patent Office has rejected claims 1-17, 20, and 21 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Particularly, the Patent Office asserts that an adequate written description is not provided for a method encompassing the identification of a "c251A→G" mutation.

The Patent Office further asserts that the claims encompass methods comprising the detection of any alteration anywhere in the SCN1A gene, and ascertaining whether the alteration is known to be SMEI-associated or non-SMEI-associated, without sufficient teaching in the specification of the detection and analysis of nucleic acid sequences comprising SCN1A alterations of such a large genus as encompassed by the claims.

Further, the Patent Office asserts that the specification does not adequately teach one of ordinary skill in the art how to identify an SCN1A mutation that is "known to be SMEI-associated" or "non-SMEI-associated."

After careful consideration of the rejections and the Patent Office's basis therefore, applicants respectfully traverse the rejections and submit the following remarks.

Initially, applicants note that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). Thus, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Patent Office to rebut the presumption. See Manual of Patent Examining Procedure (hereinafter "MPEP") § 2163.04 citing In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Further, as a matter of Patent Office practice, the burden rests upon the Patent Office to establish a *prima facie* case of a failure to comply with 35 U.S.C.

§112, first paragraph, with respect to the invention described and claimed in applicants' patent application. See Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement (hereinafter "The Guidelines"), 66 Fed. Reg. at 1105. This includes "the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims". Id. The Patent Office must establish "by a preponderance of the evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined in the claims". Id. at 1107, citing Wertheim, at page 263. The Patent Office, therefore, must have a reasonable basis to challenge the adequacy of the written description, and, in rejecting a claim, the Patent Office must set forth express findings of fact which support the lack of written description rejection.

Additionally, applicants note that there is "an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement". Id at 1105, citing Hybridtech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). With regard to the "representative number of species" necessary to describe an entire genus, applicants further note that what constitutes such a representative number is also an inverse function of the skill and knowledge in the art. Satisfactory disclosure is achieved if the skilled artisan recognizes from the disclosed species that the applicant was "in possession of the necessary common attributes or features of the elements possessed by the genus" Id. at 1106.

With regard to the Patent Office assertion that an adequate written description is not provided for a method encompassing the identification of a "c251A→G" mutation and with regard to the Patent Office assertion that the claims encompass methods comprising the detection of any alteration anywhere in the SCN1A gene, and ascertaining whether the alteration is known to be SMEI-associated or non-SMEI-associated, without sufficient teaching in the specification of the detection and analysis of nucleic acid sequences comprising SCN1A alterations, applicants

respectfully direct the Patent Office's attention to page 12, line 28, through page 14, line 16 of the subject application, which recites:

> For the diagnostic detection of novel alterations in SCN1A involved in SMEI, antibodies raised to the carboxy-terminal end of the protein would be preferable. For the diagnostic detection of SCN1A alterations previously identified to be involved in SMEI, antibody raised against the defective gene product is preferable. Antibodies are added to a portion of the patient sample under conditions where an immunological reaction can occur, and the sample is then evaluated to see if such a reaction has occurred. The specific method for carrying out this evaluation is not critical and may include enzyme-linked immunosorbant assays (ELISA), described in U.S. Pat. No. 4,016,043, which is incorporated herein by reference; fluorescent enzyme immunoassay (FEIA or ELFA), which is similar to ELISA, except that a fluoregenic enzyme substrate such as 4-methylumbelliferyl-beta-galactoside is used instead of a chromogenic substrate, and radioinmunoassay (RIA). The most definitive diagnostic assay that may be employed is DNA sequencing, and ultimately may be the only assay that is needed to be performed. Comparison of the SCN1A DNA wild-type sequence with the SCN1A sequence of a test patient provides both high specificity and high sensitivity. The general methodology employed involves amplifying (for example with PCR) the DNA fragments of interest from patient DNA; combining the amplified DNA with a sequencing primer which may be the same as or different from the amplification primers; extending the sequencing primer in the presence of normal nucleotide (A, C, G, and T) and a chain-terminating nucleotide, such as a dideoxynucleotide, which prevents further extension of the primer once incorporated; and analyzing the product for the length of the extended fragments obtained. While such methods, which are based on the original dideoxysequencing method disclosed by Sanger et al., 1977 are useful in the present invention, the final assay is not limited to such methods. For example, other methods for determining the sequence of the gene of interest, or a portion thereof, may also be employed. Alternative methods include those described by Maxam and Gilbert (1977) and variations of the dideoxy method and methods which do not rely on chain-terminating nucleotides at all such as that disclosed in U.S. Pat. No. 4,971,903, which is incorporated herein by reference. Any sequence differences (other than benign polymorphisms) in SCN1A exons of a test patient when compared to that of the wild-

> type SCN1A sequence indicate a potential SMEI-causing alteration.
>
> In a further aspect of the invention there is provided a method for the diagnosis of SMEI in a patient comprising the steps of selecting a system of assays comprising one or more assays to provide a test for the existence of an SCN1A alteration, and one or more assays to provide a test to identify the nature of the alteration, so as to determine the likelihood that it is an SMEI-associated alteration.
>
> Application of the invention has lead to the identification of a number of mutations in the SCN1A gene in individuals that have been clinically diagnosed with SMEI. This demonstrates the utility of the diagnostic assay in providing a likelihood that an individual may be affected with SMEI.

Accordingly, applicants respectfully submit that the specification of the subject application teaches methods that would allow one of ordinary skill in the art to detect an alteration in the SCN1A gene, as claimed.

With regard to the Patent Office assertion that the specification does not adequately teach one of ordinary skill in the art how to identify an SCN1A mutation that is "known to be SMEI-associated" or "non-SMEI-associated", applicants respectfully submit that after a review of the present disclosure, one of skill in the art would be able to determine whether an alteration in the SCN1A gene is known to be SMEI-associated or non-SMEI associated. Specifically, applicants point to page 6, lines 22-33 of the subject specification, which recites:

> The identification of SCN1A alterations in a patient that lead to more severe changes to the SCN1A protein (such as frameshift mutations and nonsense mutations leading to a truncated protein) increases the likelihood that the patient has SMEI. This likelihood is increased even further if it can be shown that the alteration is a *de novo* change rather than one that is inherited from the patients parents or relatives, or that the alteration in the SCN1A gene is one that has previously been associated with SMEI. The flow chart in Figure 1 illustrates one aspect of the present invention.

Applicants further point to page 41, lines 23-33 of the specification, which recites:

> The results of the screening of 26 of the 33 amplicons of the SCN1A gene are shown in Table 3. A total of 96 patients were analysed with their clinical epilepsy phenotype being hidden during the analysis. A total of 34 samples were shown to have an alteration in the SCN1A gene and of these, 28 samples had a clear SMEI phenotype based on a clinical analysis. Four of the SCN1A alterations (M1780T, R222X, R1407X, R1892X) that were identified are not shown in Table 3 as they had previously been associated with SMEI (Nabbout et al., 2003; Claes et al., 2001; Sugawara et al., 2002).

Accordingly, applicants respectfully submit that upon review of the present disclosure, one of ordinary skill in the art would readily be able to ascertain that when a particular mutation is said to be "known to be SMEI associated" or "known to be non-SMEI associated", the particular mutation has been previously associated with SMEI in the literature, or has previously been non-SMEI associated, respectively. Thus, it is believed to be with the capability of one of ordinary skill in the art to access published literature to determine whether a particular mutation is SMEI associated or non-SMEI associated.

Thus, applicants respectfully submit that the specification of the subject application as filed fully discloses the subject matter encompassed by the presently rejected claims. Therefore, applicants submit that claims 1-17, 20, and 21 comply with the written description requirement of 35 U.S.C. §112, first paragraph. Thus, applicants respectfully submit that the instant 35 U.S.C. §112, first paragraph, rejection of claims 1-17, 20, and 21 as allegedly failing to comply with the written description requirement has been addressed. Accordingly, applicants respectfully request that the instant rejection be withdrawn at this time. Allowance of claims 1-17, 20, and 21 is also respectfully requested.

IX. Response to the 35 U.S.C. §112, First Paragraph, Enablement Rejection of Claims 1-17, 20, and 21

Claims 1-17, 20, and 21 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

After careful consideration of the rejection and the Patent Office's basis therefore, applicants respectfully traverse the rejection and submit the following remarks.

Applicants initially submit that as a matter of Patent Office practice, the burden rests upon the Examiner to establish a *prima facie* case of a failure to comply with 35 U.S.C. §112, first paragraph, with respect to the subject matter described and claimed in Applicants' patent application. *See* In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971). Applicants respectfully submit that the Examiner has not met the burden of establishing a *prima facie* case of a failure to comply with 35 U.S.C. §112, first paragraph, and traverse the Examiner's rejection of claims 1-17, 20, and 21 under 35 U.S.C. § 112, first paragraph, as follows.

Applicants further submit that the appropriate standard for measuring enablement under 35 U.S.C. §112, first paragraph, is that the claimed subject matter must be enabled so that a person skilled in the art can make and use the invention from the disclosures of the specification, coupled with information known in the art, without "undue experimentation." In re Wands, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). Further, the quantity of experimentation to be performed by one of ordinary skill in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the U.S. patent application in question provides a reasonable amount of guidance with respect to the direction in which experimentation should

proceed." In re Wands, 8 U.S.P.Q.2d at 1404 (citing In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. U.S. v. Telectonics, Inc., 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989). Specific comments presented by the Examiner in view of the appropriate standard for measuring enablement under 35 U.S.C. §112, first paragraph, are addressed as follows.

Initially, the Patent Office asserts that the claims are drawn to methods for the diagnosis of SMEI in a patient, and encompass any subject organism including non-human subjects. Accordingly, the Patent Office asserts that the claims require knowledge of whether or not any particular detected mutation is known to be SMEI associated or non-SMEI associated, and further depends on the concept that any detected *de novo* mutation in the SCN1A gene is indicative of SMEI.

In response, applicants respectfully submit that the Patent Office appears to have mischaracterized the nature of the presently claimed subject matter. Particularly, the presently claimed subject matter is not directed to novel nucleic acids, but with a novel methodology. To elaborate, a conventional diagnostic test involves an analysis of a piece of DNA to establish whether or not a mutation exists, *i.e.*, if the mutation is present the diagnosis will be positive for the disease state, and if the mutation is absent the diagnosis will be negative for the disease state, depending on the nature of the disease. Generally, the test involves amplification of one single and specific portion of a gene to establish whether or not the mutation is present.

However, as disclosed in the subject application, a "patient down" perspective allows the identification of specific mutations that are causative of certain disease states. Further, SMEI does not have one single cause, hence a diagnostic test that seeks to establish the presence of absence of a mutation identified in a study based on a small group of patients would at best identify the disease only a small proportion of the patients. Further, mutations in SCN1A can be linked with other diseases, and thus these mutations are not causative or indicative of SMEI. Accordingly, as set

forth in the subject application, a conclusion cannot definitively be drawn that SMEI is always associated with a mutation in SCN1A, or that all mutations in SCN1A result in SMEI.

In view of these difficulties, a conventional diagnostic test wherein a portion of the SCN1A gene is amplified to establish the presence or absence of a particular mutation cannot be established. Rather than accept the impossibility of developing a conventional diagnostic test, the presently claimed subject matter is directed to the notion that most cases can be diagnosed by looking at the totality of the genetic landscape for SCN1A.

In the first leg of the approach, SCN1A is screened, a mutation that has been previously associated with SMEI is discovered, and a likelihood of high probability of SMEI is determined. In the second leg of the approach, SMEI is screened, a mutation that has previously been identified as one not associated with SMEI is identified, and a likelihood of low probability of SMEI is determined. In the case where the mutation proves to be neither known nor not known to have an association with SMEI, the likelihood of high/low probability of SMEI is not determined immediately, but is investigated further. In some embodiments, the specification of the subject application sets forth that after establishing whether or not the mutation has arisen *de novo* and/or whether it is a truncating mutation, the likelihood of SMEI can be set out as in Figure 1.

Accordingly, the first leg of the test can define nothing more than a conventional test if one were actually testing for a known mutation. However, this is not what occurs, because identification of a known mutation is just one possible result of the SCN1A screen. Unlike a conventional diagnostic test, in the disclosed methods, the SCN1A gene is screened for the presence of any mutation (as compared to a single and specific mutation expected in a conventional diagnostic test), and how the test proceeds depends on whether the mutation falls into the first , second, or third leg of the test.

In addition, as set forth in the specification of the subject application, the test can involve HPLC analysis and/or DNA sequencing to enable identification of

characterization of a mutation anywhere in the gene. In comparison, a conventional diagnostic test seeking to identify a specific mutation associated with a disease state will generally involve amplification of a specific sequence within the gene, often with only the desired form of the gene being amplified. If the result is negative, a negative diagnosis is entered and if the result is positive, a positive diagnosis is entered.

In comparison, in the presently claimed subject matter, there is no test for the presence or absence of any specific mutation and no diagnosis made based on the absence of any specific mutation. Applicants further submit that a great number of mutations associated with SMEI occur in the SCN1A gene, and thus the disclosed methods can be used as an aid in the determination of the likelihood of SMEI in 75% of cases.

To elaborate, as set forth in the Examples, patients with seizure disorders were studied beginning in the first year of life. A diagnosis of SMEI was made in 61 subjects by conventional means to allow the study to proceed. Of the 61 patients with SMEI, 46 were found to have a mutation in SCN1A, representing 75% of cases that can be correctly diagnosed using the methods of the present claims, and thus the chances of an appropriate diagnosis and treatment in the population in which SMEI first presents can be greatly increased. In addition, it will be appreciated that patients in the first year of life cannot communicate symptoms, and that in excess of 90% of the causative mutations arise *de novo*, with the remainder being familial in origin. Thus, it is to diagnose SMEI in the clinic at the time of onset, and yet selection of an appropriate treatment at the onset is crucial (see, for example, page 6 of the subject application). Therefore, a diagnostic test that allows the determination of the likelihood that a patient suspected of SMEI does or does not have SMEI using a non-invasive technique in 75% of infants suffering from seizure disorders and includes safeguards against false positives is a great aid in establishing appropriate treatment that would not have been possible without the presently claimed methods.

Accordingly, it is apparent from a review of the instant specification that aspects of the presently disclosed and claimed subject matter lie in the identification

of three possible categories of results upon initial screening of a patient suspected of having SMEI, and provision of steps involved in determining the likelihood of SMEI.

The Patent Office is additionally referred to Figure 1 of the present U.S. patent application, and the corresponding description of the flowchart depicted therein. The flowchart illustrates a strategy that can be used to determine the likelihood that an alteration in the SCN1A gene is responsible for SMEI. The process involves screening to identify an alteration in the SCN1A gene in a patient sample, whether the alteration is known or unknown. Then, in accordance with the flowchart, establishing whether the alteration is known to be SMEI-associated, known to be non-SMEI associated, or an unknown alteration that has been identified previously but whose association or otherwise with SMEI is uncertain. If it is a known alteration, whether it be SMEI associated or non-SMEI associated, the likelihood of SMEI can be determined, depending on which category it falls into. However, if the alteration was previously unknown, additional steps must be taken to determine the likelihood that the alteration is SMEI-associated.

Such exemplary steps are disclosed in Figure 1. Particularly, in the embodiment disclosed in Figure 1, the next step is to screen the parents and relatives for the alteration. A positive finding indicates that the mutation is inherited, and hence that there is a low probability of SMEI. A negative result in the parents or relatives suggests the mutation has arisen *de novo*, which is suggestive of SMEI. In the embodiment of Figure 1, a further step is taken to establish whether the alteration is a truncating mutation and, if so, a determination of a very high probability can be made.

Accordingly, applicants respectfully submit that the presently claimed subject matter provides a method to be employed to make a determination of the likelihood of SMEI in circumstances where screening can identify mutations known to be associated with SMEI, mutations known not to be associated with SMEI, and mutation that were previously unknown. Clearly, any and all mutations in the SCN1A subunit will fall into one of these three categories. Accordingly, a complete method

for the determination of the likelihood of SMEI is disclosed and enabled, irrespective of whether the mutation is previously known or unknown.

The Patent Office asserts that Sugawara *et al.* (2002) *Neurology* **58**:1122-1124 (hereinafter referred to as "Sugawara *et al.*") teaches that SMEI associated mutations in the SCN1A gene result in functional differences in the encoded protein such that neither Sugawara *et al.* nor the present specification teach how a mutation can be identified a priori in the SCN1A gene that is associated with SMEI or will affect the functionality of the resulting protein. In response, applicants respectfully submit that Sugawara *et al.* does not teach or suggest the determination of the likelihood of SMEI involving a decision-making tree as in the presently claimed subject matter. There is a broad suggestion at the conclusion of Sugawara *et al.* that the findings presented "will lead directly to improved diagnosis and prognosis of SMEI...", but no indication as to how this can be achieved. Thus, at best, Sugawara *et al.* appears to disclose the study of epilepsy patients to give information that allows one performing the method to ascertain whether a subject who tests positive for one of the disclosed mutations to be diagnosed as having a high probability of SMEI.

Accordingly, applicants respectfully submit that the instant 35 U.S.C. §112, first paragraph, enablement rejection of claims 1-17, 20, and 21 has been addressed. Thus, applicants respectfully request that the instant rejection be withdrawn at this time. Allowance of claims 1-17, 20, and 21 is also respectfully requested.

X. Response to the 35 U.S.C. §102(b) Rejection of Claims 1-3, 5-10, 12, 16, and 20 in view of Claes *et al.*

The Patent Office has rejected claims 1-3, 5-10, 12, 16, and 20 under 35 U.S.C. §102(b) as allegedly being anticipated by Claes *et al.* Particularly, the Patent Office asserts that Claes *et al.* teaches each and every element of the rejected claims.

After careful consideration of the rejection and the Patent Office's basis therefore, applicants respectfully traverse the rejection and submit the following remarks.

Preliminarily, applicants note that it is well settled that for a cited reference to qualify as prior art under 35 U.S.C. §102, each element of the claimed subject matter must be disclosed within the reference. "It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention." Hybritec, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986). Thus, applicants respectfully submit that for the cited reference to be an anticipation reference under 35 U.S.C. §102, the reference must disclose each and every element of the claimed subject matter.

Initially, applicants respectfully submit that independent claim 1 has been amended herein to recite "A method for determining the likelihood that a patient suspected of SMEI does or does not have SMEI comprising: (1) testing a patient sample for the existence of an alteration in the SCN1A gene of the patient, including in a regulatory region of the gene; (2) (a) terminating the process with an inconclusive diagnosis if no alteration is found; or (b) identifying the alteration; (3) ascertaining whether the alteration, when one is detected, is known to be SMEI associated or non-SMEI associated or is not known to be either; wherein (a) a diagnosis which will indicate a high probability of SMEI is made where the alteration is known to be SMEI associated; (b) a diagnosis which will indicate a low probability of SMEI is made where the alteration is non-SMEI associated; or (c) further analysis is undertaken to establish whether the alteration is a SMEI associated or a non-SMEI associated alteration. Support for the amendments to claim 1 can be found throughout the specification as filed, including particularly at page 6, lines 22-26; page 8, liens 5-17; page 14, lines 3-16; and in Figure 1. No new matter has been added.

Accordingly, applicants respectfully submit that independent claim 1 is directed to a "gene up" approach for determining the likelihood that a patient has SMEI. To elaborate, the presently claimed subject matter is directed to whether most cases of SMEI could be diagnosed by looking at the totality of the genetic landscape for the

SCN1A gene coding the alpha 1 subunit of the sodium channel. Particularly, the "gene up" approach as disclosed in independent claim 1 comprises a first leg wherein once the SCN1A gene in a patient is screened, a diagnosis of high likelihood of SMEI is entered if a mutation that has been previously identified with SMEI is discovered. In the second leg, a diagnosis of a low probability of SMEI is entered if the mutation in the SCN1A gene has been previously identified as one not associated with SMEI. In the case where the mutation is neither known nor not known to have an association with SMEI, a diagnosis is not immediately entered, but is investigated further.

Claes *et al.* does not teach each and every element of independent claim 1. Particularly, applicants submit that Claes *et al.* is directed to a study of seven Belgian patients with SMEI diagnosed according to the criteria of the Commissioner on Classification and Terminology of the ILAE. In the reference, the authors identified a mutation in each patient; four had frameshift mutations, one had a nonsense mutation, one had a splice-donor mutation, and one had a missense mutation. Thus, applicants respectfully submit that Claes *et al.* represents a "patient down" study, wherein a patient having a disease is examined to identify a specific mutation in that patient which allegedly could be a tested for in a diagnostic test.

Applicants respectfully submit that a "patient down" perspective at best allows the identification of specific mutations that are causative of certain disease states. Particularly, if the cause of the disease state is the same among all or most patients, a diagnostic test that is conventional in its nature is directly suggested by the results of the analysis of the patient group. However, applicants respectfully submit that SMEI does not have one single cause, hence a diagnostic test that seeks to establish the presence or absence of a mutation identified in a study based on a small group of patients such as that disclosed in Claes *et al.* would have limited effectiveness.

Further, applicants respectfully submit that there is no disclosure, teaching or suggestion in Claes *et al.* of taking the step of scanning the SCN1A gene for an alteration and, if one is found anywhere in the gene (rather than testing for one specific mutation), identifying it, and determining whether it has been previously

associated with SMEI, found to be non-SMEI associated, or neither (leading to further investigations to establish whether it is likely to be SMEI-associated or non-SMEI associated), as currently recited in independent claim 1.

Accordingly, applicants respectfully submit that Claes *et al.* does not teach each and every element of independent claim 1. Thus, applicants respectfully submit that the instant 35 U.S.C. §102(b) rejection of independent claim 1 has been addressed. Accordingly, applicants respectfully request that the instant rejection be withdrawn at this time. A Notice of Allowance directed to claim 1 is also respectfully requested.

Applicants further submit that claims 2-3, 5-10, 12, 16, and 20 depend from independent claim 1. Accordingly, the instant 35 U.S.C. §102(b) rejection of these claims has also been addressed. Thus, applicants respectfully request that the instant rejection be withdrawn at this time. A Notice of Allowance directed to these claims is also respectfully requested

XI. Response to the 35 U.S.C. §103(a) Rejection of Claims 11 13-15, and 17 Over Claes *et al.* in view of Wong *et al.*

The Patent Office has rejected claims 11, 13-15, and 17 under 35 U.S.C. §103(a) as allegedly being unpatentable over Claes *et al.* in view of Wong *et al.* Particularly, the Patent Office asserts that Claes *et al.* teaches each and every element of the rejected claims, except for methods of detecting alterations in gene sequences including the required limitations of the rejected claims. However, the Patent Office asserts that Wong *et al.* makes up for the cited deficiencies of Claes *et al.*

Initially, applicants submit that in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation in the references themselves to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on

applicant's disclosure. Manual of Patent Examining Procedures (M.P.E.P.) 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Furthermore, even when the combination of references teaches every element of the claimed invention, without a motivation to combine a rejection based on a *prima facie* case of obviousness is improper. In re Rouffet, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). Further, "the level of skill in the art cannot be relied upon to provide the suggestion to combine references". MPEP § 2143.01, citing Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Under these criteria and as outlined herein below, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness under 35 U.S.C. §103(a) with respect to claims 11, 13-15, and 17 over the cited references.

As discussed in detail hereinabove, applicants respectfully submit that Claes *et al.* does not teach methods of detecting alterations in gene sequences including the elements of the present claims. Applicants further submit that Wong *et al.* does not cure this deficiency. Particularly, applicants respectfully submit that in the absence of any teaching or suggestion of the "gene up" approach to diagnosis in Claes *et al.*, it is not believed that the teaching of specific methods of DNA analysis in Wong *et al.* is relevant.

Hence, applicants respectfully submit that the instant 35 U.S.C. §103(a) rejection of claims 11, 13-15, and 17 as allegedly being unpatentable over Claes *et al.* in view of Wong *et al.* has been addressed. Accordingly, applicants respectfully request that the rejection of claims 11, 13-15, and 17 be withdrawn at this time. A Notice of Allowance directed to these claims is also respectfully requested.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

A check in the amount of $455.00 is enclosed. The Commissioner is hereby authorized to charge any other fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON, TAYLOR, & HUNT, P.A.

Date: March 30, 2007 By: _____

Arles A. Taylor, Jr.
Registration No. 39,395

Customer No: 25297

AAT/PAD/omb